Current Comment

STUART C. CULLEN, M.D., *Editor*

Recovery Times of Dogs After Use of Fluorinated Anesthetic Agents

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Rapidity of recovery is an important feature involved in the use of any new anesthetic agent. Induction time is not quite so important because of the ease of producing sleep with intravenous agents. Four fluorinated anesthetic agents were therefore compared in dogs under similar conditions for their waking times. The concentrations of agent necessary for surgical anesthesia were simultaneously determined.

METHOD

Two groups of four dogs each were anesthetized in the following Latin square sequence, so that each animal could be his own control and comparisons would be more valid.

	Dog 1	*Dog 2*
Agent 1	Halopropane[1]	Methoxyflurane
Agent 2	Methoxyflurane	Fluroxene
Agent 3	Fluroxene	Halothane
Agent 4	Halothane	Halopropane
	Dog 3	*Dog 4*
Agent 1	Fluroxene	Halothane
Agent 2	Halothane	Halopropane
Agent 3	Halopropane	Methoxyflurane
Agent 4	Methoxyflurane	Fluroxene

The agents were administered with oxygen flowing at 1 liter/minute plus sufficient oxygen through the vaporizer to furnish the concentration of agent desired using a partial rebreathing circle absorption system. A cuffed endotracheal tube was inserted after the dogs had been given sleep doses of thiopental. No premedication had been given. Intermittent positive pressure was used with a mechanical respirator, inspiratory time being half expiratory time, and tidal volume being 20 ml./kg., 24 cycles per minute. Concentrations of agent were used that put the animals into "smooth" anesthesia within approximately 15 minutes. This plane of anesthesia was then maintained for 30 minutes at which time *control* blood and gas samples were taken for analysis. The blood was taken from an indwelling Cournand needle in the femoral artery. Gas samples were taken from the gas flowing to the dog at the junction of the Y piece and endotracheal tube, and from a catheter whose opening was in the trachea beyond the end of the endotracheal tube. Gas analysis was done by means of a Perkin-Elmer gas chromatograph. Catheter samples were taken at the end of an exhalation to obtain *end-tidal* gas. EEG and ECG were monitored throughout, and the EEG plane was consistently between Courtin[2] planes 3 and 4 to maintain surgical anesthesia

TABLE 1. Average *p*H values of Arterial Blood of Eight Dogs

	End of Control Period	After 60 Minutes of Smooth Surgical Anesthesia	At Extubation
Halopropane	7.44	7.40	7.34
Methoxyflurane	7.55	7.56	7.42
Fluroxene	7.59	7.51	7.43
Halothane	7.54	7.52	7.40

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TABLE 2. End-Tidal CO_2 Concentrations*

	End of Control Period %	After 60 Minutes of Smooth Surgical Anesthesia %	At Extubation %
Halopropane	0.77	0.94	1.26
Methoxyflurane	0.86	1.11	1.44
Fluroxene	0.99	1.60	2.21
Halothane	1.95	1.12	3.03

* Atmospheric pressure was 630 mm. of mercury.

TABLE 3. Concentrations of Anesthetic Agents

	End of Control Period		After 60 Minutes of Smooth Surgical Anesthesia		At Extubation
	Inhaled %	End-tidal %	Inhaled %	End-tidal %	End-tidal %
Halopropane	2.04	1.38	1.38	1.26	0.29
Methoxyflurane	1.02	0.52	0.45	0.32	0.07
Fluroxene	10.02	5.92	8.32	6.24	1.88
Halothane	1.46	0.94	1.35	0.74	0.28

as determined by pinching the web between the toes, failure to react to movements of the endotracheal tube, and the loss of the lateral canthus reflex with retention of the medial reflex. These have for years been the criteria of surgical canine anesthesia in our laboratory. This depth, according to Eger, is comparable to that used by Merkel and Eger for their MAC-1 (Minimum Anesthetic Concentration).[3] The pulse was taken regularly and frequently.

The same clinical level of anesthesia was then continued for another hour. During this period it was possible to lessen the concentration given to some extent. At the end of the 60-minute period, blood and gas samples were again withdrawn for analysis, the tidal volume was reduced to 10 ml./kg. and air was used as the respiratory gas. When the dog became sufficiently active so that he would no longer tolerate the presence of the endotracheal tube, blood and gas samples were again taken, and the animal was extubated. Time was recorded from (1) the instant of stopping the anesthetic gas, and (2) from the moment of extubation until the dog regained his righting reflex, *i.e.*, until he stood spontaneously on all fours. At least a week was allowed to elapse between any two consecutive experiments with any one animal.

RESULTS

Average *p*H values for the eight dogs and the conditions under which they were obtained are listed in table 1. End-tidal (alveolar) CO_2 values are found in table 2. These values are much lower than would be expected on the basis of the *p*H determinations whose levels were quite logical. Although it is possible that a considerable alveolar-arterial gradient exists in the anesthetized subject this could hardly account for the minimal figures observed. The concentrations of anesthetic agents listed in table 3 were determined on the same samples that contained the carbon dioxide, and they are in line with what would be expected, so relative hyperventilation may have contributed to producing these low CO_2 figures. These values obtained at extubation, after tidal volume had been halved, were increased as one might predict.

Concentrations of gas offered the animals for maintenance of anesthesia and values obtained from end-tidal (alveolar) samples are

TABLE 4. Average Waking Times After Fluorinated Anesthetic Agents, Eight Dogs.

	Agent Off to Extubation (minutes)	Extubation to All Fours (minutes)	Agent Off to All Fours (minutes)	Blood/Gas Solubility	Oil/Gas Solubility
Halopropane	110	37	147	5.8 (3)	323 (3)
Methoxyflurane	69	86	155	12 (5)	825 (4)
Fluroxene	36	15	51	1.37 (5)	48 (5)
Halothane	46	28	74	2.4 (5)	224 (6)

Reference numbers in parentheses.

listed in table 3. The barometric pressure in Denver is 630 mm. of mercury, so the percentage values are about 76/63 as high as though the values had been calculated for sea level. The high concentrations of fluroxene required were surprising.

The period required for waking is listed in table 4. As might have been expected [5] the waking times were in the same order as the blood/gas and oil/gas solubilities, although they were not closely proportional in this small series. Inasmuch as the concentrations offered the dog were greater than the exhaled concentrations, the animals were still absorbing the anesthetic gas and had not actually reached a *steady state* at the end of the anesthetic period, even though the anesthesia was clinically smooth. Generally speaking, fluroxene and halothane which have lower solubilities permitted reasonably rapid waking, while halopropane and methoxyflurane kept the dogs asleep for a considerable time.

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Impurity in Stored Halothane

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Cohen *et al.*[1] suggested in September, 1963 that the use of copper vaporizers in this country as opposed to nickel-plated or glass vaporizers in many other countries may be significant. They identified one of the impurities in freshly opened and stored halothane as a halogenated butene, 2,3-dichloro-1,1,1,4,4,4-hexafluorobutene-2. These authors reported further that this drug was toxic to dogs when inhaled in anesthetic concentrations, and to rats when exposed to a 0.01 per cent concentration for four hours. They noted that when halothane was refluxed in the presence of copper filings in an oxygen atmosphere the concentration of the halogenated butene increased.

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These investigators observed that under their conditions of clinical usage the concentration of this contaminant had increased from 0.01 per cent to 0.1 per cent during a five-day period while stored in a Copper Kettle vaporizer. The implication in their presentation was that the chemical reaction produced in their laboratory was duplicated in the copper vaporizers, and that under clinical conditions 2,3-dichloro-1,1,1,4,4,4-hexafluorobutene-2 was formed from halothane. They stated, in addition, that fractional distillation resulted in a *radical* enrichment of the content of the compound in the residual volume.

The above report prompted us to evaluate the practice of storing halothane in our own institution, and to determine the amount of contamination in available samples. The residual halothane in each of eight anesthetic